ABBOTT LABORATORIES
Global Pharmaceutical Regulatory Affairs

Douglas L. Sporn
Divisional Vice President
Regulatory Intelligence and FDA Liaison Office
Global Scientific & Medical Affairs
Abbott Laboratories

Abbott FDA Liaison Office
1700 Rockville Pike, Suite 310,
Rockville MD 20852

Tel: 301-255-0080 Fax: 301-255-0090
E-mail : doug.sporn@abbott.com

April 25, 2005

Division of Dockets Management (HFA-305)
The Food and Drug Administration
5630 Fishers Lane, room 1061,
Rockville, MD 20852

Re: **Docket No. 2005D-0004. Draft Guidance on Nonclinical Safety Evaluation of Drug Combinations.**

Abbott Laboratories (Abbott) is pleased to have the opportunity to comment on the Nonclinical Safety Evaluation of Drug Combinations Draft Guidance, published in the Federal Register on January 26, 2005.

We thank the Agency for their consideration of our attached comments. Should you have any questions, please contact Ivone Takenaka, Ph.D. at (301) 255-0080 or by FAX at (301) 255-0090.

Sincerely,

Douglas L. Sporn

Douglas L. Sporn

Abbott

Comments on Draft Guidance on
Nonclinical Safety Evaluation of Drug Combinations

Docket No. 2005D-0004

The following comments on the above-mentioned Draft Guidance are provided on behalf of Abbott Laboratories.

II. NONCLINICAL STUDIES FOR A COMBINATION OF TWO (OR MORE) PREVIOUSLY MARKETED DRUGS

A. Safety Considerations

Lines 62–104 provide the following list of 9 "factors relevant to the safety" of a combination of two or more previously marketed drugs.

1. *Information available on prior human experience with the combination. FDA recommends that the sponsor provide a summary of the available data in humans (if any) on the use of the combination. FDA also encourages the sponsor to provide copies of any relevant published studies in humans (or animals). Such reports may not provide definitive safety data, but they may provide some measure either of assurance or reasons for concern.*

2. *Information known about the individual drugs in animals and humans and concordance of pharmacokinetics (PK), pharmacodynamics (PD), and toxicologic effects in animals with the analogous data for humans.*

3. *Possibility of a pharmacodynamic interaction. Drugs may exhibit affinity for the same receptors or may produce similar effects on physiologic function, related or not to their mechanism of action.*

4. *Possibility of a pharmacokinetic interaction. A pharmacokinetic interaction can manifest in several ways, some of which can be monitored in vivo and some of which cannot. One drug product may alter the absorption or excretion of another product, change its distribution into one or more tissues, or change its pattern or rate of metabolism. Drugs may compete for serum protein binding, resulting in an increase in circulating free levels and tissue uptake of one drug.*

5. *Possibility of a toxicologic interaction (i.e., that the target organs for toxicity are similar for each drug). This situation may result in a lowering of the previously determined no-effect doses for one or both drug products and/or more severe toxicities in the affected organs. FDA will consider all known toxicology on the product (e.g., general toxicity, reproductive toxicity, carcinogenicity, and safety pharmacology studies (cardiovascular, central nervous system or CNS, respiratory)).*

6. *Margin of safety for each drug product. If one or more of the drugs has a narrow margin of safety (i.e., causes serious toxicity at exposures close to the predicted clinical exposure), then the possibility of drug interaction is of particular concern, especially if the toxicity is not reversible or cannot be monitored clinically.*

7. *Possibility that the drugs compete for or alter the activity or endogenous levels of the same enzymes or other intracellular molecules (e.g., co-administration of two prooxidants could deplete endogenous levels of glutathione).*

8. *Possibility of a chemical interaction. One drug may chemically modify another drug (e.g., one drug may oxidize, methylate, or ethylate the other drug). This could result in new molecular entities with new toxicities.*

9. *Possibility that one drug is compromising the effectiveness of another drug for a lifesaving therapy.*

Comment: Several items on the list appear to duplicate others in content and principle.

Recommendation: The list may be shortened and simplified by combining or deleting items that address the same principle. We suggest the following revised list below, which combines factors 1 and 2 (which deal with similar issues), and preserves items 3, 4, 5, and 8, which describe the four types of interaction (PK, PD, toxicologic, and chemical). Items 6, 7, and 9 are deleted because they simply paraphrase the concepts embodied in the description of the interaction types that should be considered.

1. Information available on prior human experience with the combination, including information known about the individual drugs in animals and humans as well as concordance of pharmacokinetics (PK), pharmacodynamics (PD), and toxicologic effects in animals with the analogous data for humans. FDA recommends that the sponsor provide a summary of the available data in humans (if any) on the use of the combination. FDA also encourages the sponsor to provide copies of any relevant published studies in humans (or animals). Such reports may not provide definitive safety data, but they may provide some measure either of assurance or reasons for concern. *[This combines previous items 1 and 2]*

2. Possibility of a pharmacodynamic interaction. Drugs may exhibit affinity for the same receptors or may produce similar effects on physiologic function, related or not to their mechanism of action.

3. Possibility of a pharmacokinetic interaction. A pharmacokinetic interaction can manifest in several ways, some of which can be monitored in vivo and some of which cannot. One drug product may alter the absorption or excretion of another product, change its distribution into one or more tissues, or change its pattern or rate of metabolism. Drugs may compete for serum protein binding, resulting in an increase in circulating free levels and tissue uptake of one drug.

4. Possibility of a toxicologic interaction (i.e., that the target organs for toxicity are similar for each drug). This situation may result in a lowering of the previously determined no-effect doses for one or both drug products and/or more severe toxicities in the affected organs. FDA will consider all known toxicology on the product (e.g., general toxicity, reproductive toxicity, carcinogenicity, and safety pharmacology studies (cardiovascular, central nervous system or CNS, respiratory)).

5. Possibility of a chemical interaction. One drug may chemically modify another drug (e.g., one drug may oxidize, methylate, or ethylate the other drug). This could result in new molecular entities with new toxicities.

B. Nonclinical Study Recommendations

Lines 108-111 and Lines 144-147:

Lines 108-111:

"After evaluating the available data on the individual drug products and the potential for drug interaction, if there is no evidence to suggest a possible interaction, direct assessment of the combination by testing in animals may not be needed ***before the initiation of phase 1 clinical studies****."*

Lines 144 – 147:

"FDA may recommend that additional nonclinical studies do not need to be conducted ***before testing in humans or during Phase 1*** *(Boxes 2 to 3). The Agency's recommendation to conduct nonclinical studies for further development of the combination will depend on what is learned from initial studies in humans or what is known from prior human use of the combination."*

Comment:

The draft guidance discusses recommendations *"...before the initiation of phase 1 clinical studies*." In the case of proposed combinations of two marketed products, however, it is not uncommon nor unreasonable for sponsors to plan to enter a phase 3 program directly or concurrently with additional evaluations that typically are conducted in phase 1. This is especially true when the doses and duration of therapy are similar to those for the individual components of the combination.

Recommendation: Specific reference to phase 1 in this context should be deleted. The guidance should simply refer to clinical studies or testing in humans without stipulating the phase of such studies.

Lines 165 – 171:
"Sometimes one of the drugs proposed for the combination will be much more toxic in animals than in humans, such that animals cannot tolerate the combination at doses that produce exposure relevant to the anticipated clinical exposure (e.g., some nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics). In those cases, general toxicity studies of the combination could be conducted at a dose giving less exposure than that achieved with the recommended clinical dose of the more toxic drug product, provided that a maximum tolerated dose is achieved in the animals."

Comment:
This general statement is repeated at lines 208-214 and lines 268-273 in the discussion of combinations involving an approved drug and an NME or combinations of two or more NMEs, respectively. For development of combination products in which the active ingredients are all separately approved products with a marketing history that reflects extensive human exposure, the necessity for non-clinical toxicity studies of the combination is not adequately justified in the draft guidance. Figure B (lines 392-394) indicates that such studies should "usually" be conducted. Similarly, where combinations of NMEs are involved, Figure C (lines 422-424) appears to recommend that, even when appropriate toxicity studies of the individual active ingredients have been conducted, non-clinical studies of the combination are recommended.

Recommendation: The recommendation for conducting non-clinical studies using the combination of active ingredients should include a rationale for such studies and discussion of whether there are alternative approaches that may be considered.

III. NONCLINICAL STUDIES FOR A COMBINATION OF DRUGS WHEN ONE OR MORE IS PREVIOUSLY MARKETED AND ONE IS A NEW MOLECULAR ENTITY

A. General Toxicology Studies

Lines 201-202 and 254-256: *"Depending on the duration of the proposed therapy, FDA recommends that a sponsor conduct a bridging study of up to 90 days with the combination in the most appropriate species."*

Comment:
This statement is unclear. As written, this sentence may be interpreted to state that whether or not FDA recommends a bridging study depends on the duration of the proposed therapy. Alternatively, the intention may be to say that the length of the bridging study depends on the duration of the proposed therapy. In addition, the term "bridging study" may not be universally understood.

Recommendation: (1) Revise the sentence to make the intended meaning clear; (2) Include a brief definition of what is meant by "bridging study" in this context.

Lines 225–228 and 277–280
"Valuable data may be obtained from studying the combination in appropriate animal models of efficacy. For example, there are situations in which one drug has been shown to alter the efficacy of the second drug. This information is especially important if one or more of the drugs in the combination is for a serious or life threatening indication."

Recommendation: A brief additional summary of the rationale for conducting studies in animal models of efficacy for combinations such as MD-NME and NME-NME that have already been extensively studied individually, would provide needed clarity.

Figures A and C – *Box 6. Metabolic interaction identified?*

Comment:
The chart seems to recommend that if a metabolic interaction has not been identified, one can proceed with clinical study.

Recommendation: Delete the word "identified?" and change to simply "6. Metabolic interaction".